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Passive smoking and childhood asthma

Urinary cotinine levels in children with asthma and in referents

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Passive exposure to tobacco smoke was assessed in children with asthma (age 3-15) and in referents. There was statistically significantly ($P < 0.0005$) higher excretion of the nicotine metabolite, cotinine, in the urine of 49 children with asthma (geometric mean 10 ng/ml) compared with 77 referents (4.8 ng/ml). Maternal smoking was statistically [redacted]ficantly more prevalent among the asthmatics than among the referents (relative risk: [redacted]R = 2.6, 95% CI = 1.2-5.3). In conclusion, the exposure to environmental [redacted]co smoke in asthmatic children was higher than among healthy children, indicating [redacted] passive smoking may be a predisposing and/or aggravating factor for childhood [redacted]ma.

Key words: childhood asthma; cotinine; involuntary; passive smoking; predisposing factor.

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CLINICAL ASPECTS

Parental smoking cessation is of clinical importance in the asthma treatment program. Passive exposure to tobacco smoke was assessed in children with asthma and in referents. The excretion of the nicotine metabolite cotinine in urine was higher in children with asthma than in healthy children, which gives further evidence of a relationship between passive smoking and childhood asthma.

It is well known that (active) smoking is a main predisposing factor in the development of bronchial hyperreactivity and it is also known that tobacco smoke (i.e. passive smoking) irritates the bronchi in asthmatic patients (2). Tobacco smoke is probably the most important air pollution in the home, and children, especially in the Nordic countries, spend a lot of time indoors. Several studies have shown a higher frequency of respiratory infections in children of smokers (15). Further, exposure to tobacco smoke damages the airway epithelium and increases its permeability (8), which is hypothesized to be one mechanism in the development of allergy. There is some evidence of an association between passive smoking and obstructive respiratory disease in children. Thus, in a study of children at 8 and 13 years, maternal smoking was a powerful predictor of wheezing (11). Moreover, in 1986, Murray et al. (12), showed an increased severity of asthma in asthmatic children of smokers compared with those of non-smokers. However, the association between passive smoking and asthma is not consistent in the various studies.

Cotinine (the major nicotine metabolite) has been shown to be the biological marker of choice for passive smoking (9). The aim of this study was to investigate the relationship between passive smoking and asthma in children by using this objective measurement of passive exposure to tobacco smoke.

Table 1.

Cotinine levels in urine of asthmatic children and referents in relation to parental smoking habits

Parental smoking	Asthma cases Cotinine levels (ng/ml)			Referents Conine levels (ng/ml)		
	N	Geometric mean	Range	N	Geometric mean	Range
Neither	12	2.0	0.8-9.0	30	2.0	0.4-19
One parent	23	13 *	1.9-210	29	8.1	1.1-36
only father	6	8.1	4.2-20	16	5.8	1.1-26
only mother	17	15	1.9-210	13	12	2.9-36
Both	14	24 ***	5.6-56	18	9.4	1.1-44
Total	49	10 ***	0.8-210	77	4.8	0.4-44

*; *** Statistically significant differences compared with referents ($P < 0.05$; $P < 0.001$).

MATERIAL AND METHODS

Subjects

Forty-nine consecutive new cases of children with asthma (mean age 7.5 years, range 3-15) were seen during February-April 1988 at the Department of Pediatrics, Malmö General Hospital. The diagnosis of asthma was based on clinical history (i.e. recurrent episodes of cough and wheezing), and examination. At the first admittance (usually with a note of referral), a urine sample for cotinine analysis was collected. One parent was asked about both parents' smoking habits by the physician. A non-smoker was defined as a person who had never smoked or had stopped smoking more than 0.5 years ago. The number of cigarettes smoked daily (1 g of pipe tobacco was approximated to equal one cigarette) was recorded.

A referent group, from two schools, was examined during October-November 1987. All pupils and parents were asked to participate, but there was a non-response of 52%. Thus, the population sample consisted of 77 children (mean age 8.9 years, range 7-10). One parent of each child was questioned on the telephone by a nurse about both parents' smoking habits. All parents filled out a questionnaire concerning respiratory symptoms; none of the children had asthma.

The study was approved by the Ethics Committee of the Lund University.

Measurement of passive exposure to tobacco smoke

A developed capillary gas chromatographic (GC) method, using selective-ion monitoring (SIM) with deuterium labeled cotinine as internal standard, was used for the determination of cotinine in urine (17). The reproducibility of the method was good. The coefficient of variation (CV), when analysing 12 different standard samples in urine at a concentration of 5 ng/ml was 5.2%. Because there may be seasonal differences in the passive exposure to tobacco smoke (e.g. variations in room ventilation and being indoors) no urine samples were obtained during summer.

Statistics

The cotinine values were non-normally distributed. Thus, for comparison between groups (asthmatic and referents) logarithmic transformation of the cotinine values was performed. Comparisons between groups were made with t-test and Mann-Whitney U-test. Kruskal-Wallis 1-way ANOVA test was used for comparisons within groups. Kendall's tau C was used to calculate the association between parental smoking habits and cotinine levels in urine.

RESULTS

Asthmatics versus referents

In the asthmatic children, the prevalence of smoking among parents (mother and/or father) was not statistically significantly higher than among the referents (76 % and 61 %, respectively; relative risk = rr = 1.97; 95 % confidence interval 0.90–4.35; Table 1). However, maternal smoking was more prevalent among asthmatics (63 % and 40 %, respectively; rr = 2.56; 95 % CI = 1.23–5.32; etiologic fraction (EF) = 0.38).

The intensity of smoking (= number of cigarettes smoked by the parents/day) was on average, 14.2 (father 5.7; mother 8.5) for the asthmatics and 10.6 (father 5.3; mother 5.3) for the referents. This difference was statistically significant for maternal smoking (Mann-Whitney U-test; $P < 0.03$), but not among fathers, nor both parents. No significant differences in the intensity of smoking were seen if only smokers were taken into account.

There was a statistically highly significant difference between the cotinine levels in children of smokers compared with children of non-smokers, for both asthmatics and referents (geometric means: asthmatics: 2.0 and 16.4; referents: 2.0 and 8.6, $P < 0.00001$; Kruskal-Wallis 1-way Anova; Table 1). There were highly significant associations between the number of smokers and cotinine levels [Kendall's tau C = +0.70 for the asthmatics ($P < 0.00001$), and +0.55 for the referents ($P < 0.00001$)]. If, only one parent smoked, the mother's smoking habits had greater influence on the cotinine level than the father's for both asthmatics and referents; however, these differences were statistically significant only for the referents ($P < 0.01$; $t = 3.6$ and $P = 0.1$; $t = 1.7$ respectively).

The cotinine levels in the urine of asthmatic children were significantly higher than in those of the referents (Table 1, $P < 0.0005$). Further, the difference was present in all parental groups, except the non-smoker group; it was statistically significant among the "one parent" group ($P < 0.05$) and the "both parent" group ($P < 0.001$).

There were 19 asthma cases and 10 referents with cotinine values ≥ 20 ng/ml (without the range for the "neither-parent" exposed group: rr = 4.2; CI = 1.8–9.9).

DISCUSSION

In the present study, exposure to environmental tobacco smoke in asthmatic children was higher than among healthy children, as indicated by the prevalence and intensity of smoking in mothers, and the cotinine levels in urine in the children. [illegible]

This is in accordance with earlier studies. Thus, Cogswell et al. (3), showed a significantly higher prevalence of wheezing in 5-year-old children of smokers, compared with children of non-smokers, in a prospective study of children of atopic parents. Results by other investigators (12) indicated, that asthma symptom scores were higher in asthmatic children of smokers than among asthmatic children of non-smokers. McConnochie et al. (11) in a cohort study showed that maternal smoking was a strong predictor of wheezing at age 13. In accordance with this it is interesting to note that in the present study, maternal smoking was significantly more prevalent among asthmatics than among referents. The highest cotinine values (concentrations ≥ 30 ng/ml) were found among children of mothers who smoked (18 asthma and 4 referents); however, of these, seven also had a father who smoked.

One possible mechanism causing asthma may be that passive smoking predisposes to respiratory infections (4, 15), which, in turn, damages the respiratory epithelium. Also, the repair of the inflammatory changes caused by infections, may not be complete because of the continuous exposure to tobacco smoke. Thus, in a prospective study of atopic babies, the wheezing tendency decreased in children of non-smoking parents, compared with children of smokers (5). Accordingly, passive smoking appears to aggravate the state of bronchial [illegible]

other possible effect of passive smoking is to increase the permeability in the airways, which may increase the possibility for allergens to reach immunoreactive cells (8, 10, 20). Also, an allergy to some of the components in tobacco smoke has been proposed (1).

The non-response rate was high among the eligible referents. Thus, it is possible that relatively more smokers avoided joining the study. However, this is unlikely as in Sweden at the time of the study, the prevalence of smoking was 27% among both men and women (13), which is lower than in the present referents (44% and 40%, respectively). Also, as there are regional differences in smoking (18), there could be a systematic difference between the areas from where the asthmatics and referents were recruited.

The cotinine levels in our referents are in accordance with other studies of healthy children. Thus, in a study by Greenberg et al. (6) of infants under 1 year, the median value in "exposed infants" was 7.2 ng/ml. Greenberg et al. (7), also studied infants with a mean age of 18 days; the median level in children, "who excreted cotinine" was 9 ng/ml. Rylander et al. (16) found a median of 9.7 ng/ml in "4-year old children with smoking parents" and a median of 3.8 ng/ml in "non-exposed" children. The levels in some of the present asthmatic children were even higher than in adults exposed experimentally to environmental tobacco smoke (approx. 35 ng/ml (17)).

The higher cotinine levels in asthmatic children may be because passive smoking is a risk. However, an alternative explanation could be that children with asthma have a higher uptake of nicotine from the lung. Thus, we have earlier seen higher lead levels in blood in children of smokers than in those of non-smokers (19), probably due to a small airways dysfunction. However, in the present study, the cotinine levels in healthy and asthmatic children of non-smokers did not differ, which indicates that asthma is not the cause of increased cotinine excretion.

Cotinine is particularly useful in the study of children, as cotinine has a long biological half-life in children (37–160 h (14)). Cotinine levels should be valuable markers in future epidemiological studies of passive (or active) smoking as a risk factor.

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